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Selective Benefit of Donepezil on Oral Naming in Alzheimer's Disease in Men Compared to Women

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To the Editor:

Donepezil is a widely prescribed treatment for patients with probable Alzheimer's disease. Although it is accepted that donepezil can slow the decline of cognitive functioning in various stages of Alzheimer's disease,¹ sex differences affecting its efficacy are often omitted from a prescribing rationale.

We examined data from a larger study testing the effect of donepezil on cognitive functioning as well as awareness of cognitive deficits in probable Alzheimer's disease (12 participants, [7 women; 5 men] diagnosed with probable Alzheimer's disease²). All subjects were neuropsychologically evaluated with the Mini-Mental State (MMSE),³ the Boston Naming Test (BNT),⁴ and the Hopkins Verbal Learning Test (HVLT).⁵

Following a baseline evaluation, subjects were randomized to one of two double-blind crossover groups. In Group 1, 7 subjects (5 women; 2 men) received donepezil 5 mg/day for 2 months, and then received placebo for 2 months. In Group 2, 5 subjects (2 women; 3 men) received placebo for 2 months, and then donepezil 5 mg/day for 2 months. At the end of the four-month crossover treatment period, all subjects returned for neuropsychological re-assessment.

A therapeutic effect of donepezil on cognition in probable Alzheimer's disease was previously reported in studies examining aggregate memory, orientation, attention, reasoning, language and praxis performance.¹⁻⁶ This previous research suggested that global cognitive functioning, including naming and language indices improved in probable Alzheimer's disease patients taking this medication.¹ Data from our small group confirmed a specific therapeutic effect on donepezil on picture naming performance on the BNT⁴ (mean on=71.9, SD 21.81; mean off=64.8±21.52). Within-subjects repeated-measures ANOVA revealed significant main effect of drug, $F(1,11)=17.405$, $P<.01$, partial $\eta^2=0.64$). However, we also observed significant interaction of drug and gender in performance on the BNT (mean male on=75.3±23.76; mean male off=61.2±25.13; mean female on=69.5±21.89; mean female off=67.3±20.23; $F(1,11)=9.191$, $P<.05$, partial $\eta^2=0.48$.) (Table 1).

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Whether severity accounts for the sex difference in this study is unclear. Men may have had more severe symptoms, indicated by lower MMSE scores (men's mean=18.4±7.127; women's mean=21.714±6.237), but since men actually performed better on the BNT and the HVLT at baseline, we do not think this explains the sex difference in oral naming response to donepezil.

Cholinesterase inhibitor treatment, including donepezil, has been reported to be more effective in men in previous studies of humans with probable Alzheimer's disease,^{7,8} and in animal models of memory disorders.^{1,2}

In a short-term (three-month) treatment study MacGowan and colleagues⁸ found that performance on MMSE was more stable or positively affected by men on tacrine (76%) than women (52%). In a logistic regression, sex emerged as the only significant predictor of response to cholinesterase inhibitor treatment with a 73% greater response rate for men than women.⁸ Animal studies have indicated various reasons why cholinesterase inhibitors may be more successful in males than females, including the presence of testosterone, synaptic protein content, acetylcholinesterase activity, levels of acetylcholine, brain atrophy rates, the presence of the APOE *E4 alleles or different optimal dosage levels.^{7,8}

If donepezil and other cholinesterase inhibitors are more effective in men than they are in women, this is of obvious importance in disorders like probable Alzheimer's disease, of which the majority of sufferers are female. It may also be of relevance, however, for treatment of other cognitive dysfunction, for example the treatment of memory disorders due to brain injury⁹ and post-stroke aphasia.¹⁰ A difference in expected therapeutic effect by sex may indicate that different dosing regimens should be considered for female compared with male patients for memory and cognitive symptoms. Future research should also address whether sex differences may differently affect distinct cognitive domains, since sex differences in therapeutic effect may interact with underlying population differences in cognitive skills such as verbal memory or visuospatial performance.

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Table 1

Performance on Neuropsychological Tests for Probable Alzheimer's Disease Participants in the Current Study*

Women (n=7)	MMSE[†]	BNT[‡]	HVLT[§]
Mean percent correct off drug (SD)	72.4 (6.24)	69.8 (0.13)	17.8 (0.14)
Mean percent correct on drug (SD)		70.8 (0.210)	21.7 (0.110)
Men (n=5)	MMSE[†]	BNT[‡]	HVLT[§]
Mean percent correct off drug (SD)	61.3 (7.13)	71.4 (0.23) [¶]	35.3 (0.23)
Mean percent correct on drug (SD)		75.70 (0.190) [¶]	44.80 (0.20)

* Participants were only given MMSE on baseline visit.

[†] MMSE score of 30

[‡] BNT short form score of 30

[§] HVLT total for spontaneous recall of 36

[¶] $P < .01$

MMSE=Mini-Mental State Examination; BNT=Noston Naming Test; HVLT=Hopkins Verbal Learning Test.